REMARKS/ARGUMENTS

The Pending Claims

Claims 1-5 and 19-25 are pending and directed to methods for determining toxicity or non-toxicity (claims 1-15 and 19-25) to the heart of an anthracycline-type anticancer chemotherapeutic agent.

Amendments to the Claims

The claims have been amended to point out more particularly and claim more distinctly the invention. Claim 1 has been amended to recite particular steps. The amendment to claim 1 is supported by the specification at, for example, page 6, lines 1-16; page 9, line 31, through page 11, line 16; and Examples 1 and 2. Claim 2 has been amended to retain proper antecedent basis in view of the amendment to claim 1.

Claims 6-18 have been canceled.

Claims 19-25 are new, and are supported by the specification at, for example, page 4, lines 10-15; page 6, lines 5-9; page 9, line 31, through page 11, line 16; and Examples 1 and 2.

No new matter has been added by way of these amendments.

Summary of the Office Action

The Office Action objects to claim 1 for allegedly containing informalities. The Office Action rejects claims 1-5 and 14-18 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office Action also rejects claims 14-18 under 35 U.S.C. § 101.

The Office Action rejects claims 1-18 under 35 U.S.C. § 102(b) as allegedly anticipated by each of Petzold et al. (*European Journal of Cardio-thoracic Surgery, 19*: 859-864 (2001)) and Watanabe et al. (*Clinical Biochemistry, 34*: 257-263 (2001)). Additionally, the Office Action rejects claims 1-18 under 35 U.S.C. § 103(a) as allegedly obvious in view

of Watanabe et al. and Sayed-Ahmad et al. (*J. Egyptian Nat. Cancer Inst., 12:* 275-281 (2000)).

Reconsideration of these objections and rejections is hereby requested.

Information Disclosure Statement

The Office Action indicates that it did not receive a copy of reference AG, which was submitted with the Information Disclosure Statement filed December 7, 2004. Applicants herein submit a second copy of Robers et al., *Clinical Chemistry, 44(7)*: 1584-1567 (1998)) (reference AG), as well as a copy of the return postcard from the U.S. Patent and Trademark Office (USPTO), which acknowledges the receipt of reference AG by the USPTO on December 10, 2004.

Applicants respectfully request a copy of the Examiner-initialed Form PTO-1449 that confirms the Examiner's consideration of reference AG.

Discussion of the Claim Objection

The Office objects to claim 1 for the omission of "a" between "from" and "human" in lines 3-4. Claim 1 has been amended to clarify the claim language. Therefore, the claim objection is moot and should be withdrawn.

Discussion of the Section 112, Second Paragraph, Rejections

The Office contends that claim 1 does not contain sufficient antecedent basis for "the blood" in claim 1. Claim 1 has been amended to clarify the claim language.

The Office contends that claims 1-5 are indefinite for omitting essential method steps. Claim 1 has been amended to recite particular method steps, including obtaining a sample from a human to whom has been administered an anthracycline-type anticancer chemotherapeutic agent, measuring the level of human H-FABP protein in the blood sample, comparing the measured level of human H-FABP protein with a standard level of human H-FABP protein, and determining toxicity to the heart of the anthracycline-type anticancer

chemotherapeutic agent in the human based on the comparison of the measured level of human H-FABP protein with the standard level of H-FABP protein.

The Office contends that claims 14-18 omit essential method steps. Claims 14-18 have been canceled.

For the foregoing reasons, Applicants believe that the Section 112, second paragraph, rejections are moot and request the withdrawal of the rejections.

Discussion of the Section 101 Rejection

The Office rejects claims 14-18 because the claims allegedly recite a use without setting forth steps involved in the process. Claims 14-18 have been canceled. Accordingly, the Section 101 rejection is moot and should be withdrawn.

Discussion of the Section 102(b) Rejections

The Office contends that claims 1-18 are anticipated by each of Petzold et al. and Watanabe et al. The Office contends that each of Petzold et al. and Watanabe et al. teaches a method that comprises detecting human hFABP protein in the blood obtained from humans. These rejections are traversed for the following reasons.

The inventors discovered that cardiotoxicity of an anthracycline-type anticancer chemotherapeutic agent correlates with an increased level of H-FABP protein in the blood of a human undergoing therapy with the anthracycline-type anticancer chemotherapeutic agent. The pending claims, as amended, are directed to methods for determining the toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent. In general, a blood sample is obtained from a human to whom was administered an anthracycline-type anticancer chemotherapeutic agent. The level of human H-FABP protein in the blood sample then is measured and compared to a standard level of human H-FABP protein. The comparison of the measured level of human H-FABP protein to the standard level of human H-FABP protein allows for a determination of whether the anthracycline-type anticancer chemotherapeutic agent is toxic or non-toxic to the heart of the human.

Petzold et al. discloses a method of diagnosing myocardial damage in coronary artery bypass grafting by detecting H-FABP protein in blood obtained from humans. Watanabe et al. discloses a method of detecting acute myocardial infarction by detecting H-FABP protein in blood obtained from humans. Petzold et al. and Watanabe et al. do not teach or suggest a method for determining toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent, wherein, for example, "obtaining a blood sample from a human to whom was administered an anthracycline type anticancer chemotherapeutic agent" or "determining toxicity to the heart of the anthracycline-type anticancer chemotherapeutic agent in the human based on the comparison of the measured level of human H-FABP protein with the standard level of H-FABP protein," as required by the pending claims.

Since Petzold et al. and Watanabe et al. do not teach or suggest every element of the pending claims, these references do not anticipate the subject matter of the pending claims. Accordingly, Applicants request the withdrawal of the anticipation rejections.

Discussion of the Section 103(a) Rejection

The Office contends that claims 1-18 are obvious over the combination of Watanabe et al. and Sayed-Ahmad et al. The Office contends that Watanabe et al. discloses a method of detecting human H-FABP protein, but does not explicitly teach a method for determining the toxicity of an antracycline-type chemotherapeutic agent. However, the Office contends that Sayed-Ahmad et al. discloses a method of determining a correlation between H-FABP and doxorubicin cardiotoxicity by measuring the amount of H-FABP mRNA expression after single and different cumulative dose levels of doxorubicin. The Office contends that Sayed-Ahmad et al. teaches that chronic administration of doxorubicin resulted in a significant decrease in H-FABP mRNA expression, thereby suggesting that doxorubicin-induced cardiotoxicity is due to the inhibition of H-FABP. Therefore, the Office considers that it would be obvious to combine the teachings of Watanabe et al and Sayed-Ahmad et al. in order to arrive at the inventive methods.

In order to establish a *prima facie* case of obviousness with respect to a claim, at least two criteria must be met: (1) the prior art references must suggest to one of ordinary skill in the art to make the subject matter defined by the claims in issue and (2) the prior art references must provide one of ordinary skill in the art with a reasonable expectation of

success in so making the subject matter defined by the claims in issue. Both the suggestion and the reasonable expectation of success must be found in the prior art references, not in the disclosure of the patent application in issue. See, e.g., *In re Vaeck,* 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

As discussed above, the pending claims are directed to methods of determining the cardiotoxicity associated with the administration of an anthracycline-type anticancer chemotherapeutic agent in a human, wherein an increased amount of H-FABP protein in the blood as compared to a standard level of H-FABP protein is an indicator of cardiotoxicity. In contrast, Sayed-Ahmad et al. discloses that the amount of H-FABP mRNA in tissue was decreased after administering the anthracycline-type anticancer chemotherapeutic agent, doxorubicin, to a rat. Therefore, the method of Sayed-Ahmad et al. differs from the inventive methods in several important respects: the method of Sayed-Ahmad et al. involves determining the amount of H-FABP mRNA (in contrast to protein) in tissue (in contrast to blood) in a rat (in contrast to a human), wherein a decrease in the level of mRNA (in contrast to an increase in the level of H-FABP protein) correlates with toxicity.

There is no teaching or suggestion in either Watanabe et al. or Sayed-Ahmad et al. that toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent correlates with an *increase* in the level of H-FABP *protein* in the *blood* of a *human.* Therefore, one of ordinary skill in the art would not have envisioned the claimed methods, which utilize an increased amount of H-FABP protein as an indicator of cardiotoxicity caused by an anthracycline-type anticancer chemotherapeutic agent, based on the cited references. Furthermore, one of ordinary skill in the art would not have had a reasonable expectation of success in developing the claimed methods, since Sayed-Ahmad et al. indicates that a *decreased* level of H-FABP is correlated with toxicity.

For these reasons, Applicants respectfully submit that the inventive methods defined by the pending claims would not have been obvious in view of the cited references, and Applicants request the withdrawal of the obviousness rejection.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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